

REMARKS

Claims 1, 2, 21 and 30-33 are pending. Claims 30-33 are withdrawn from consideration by the Examiner. Claims 1 and 2 are amended herein. Support for the amendments is discussed herein below. The amendments add no new matter.

Claim Objection:

Claim 1 is objected to as encompassing non-elected subject matter because it “continues to recite SEQ ID NO: 2-12, which are non-elected.” While applicants disagree with the restriction on the basis that it does not present an undue burden to examine claims drawn to SEQ ID NOs 1-12, claim 1 is amended herein to remove reference to SEQ ID NOs 2-12.

Rejection under 35 U.S.C. §112, Second Paragraph:

Claim 1 is rejected under 35 U.S.C. §112, second paragraph as indefinite and vague in the recitation of “neuronally active.” The Office Action asks “what does this phrase mean?”

While the specification makes it clear what is meant by the phrase, in the interest of advancing prosecution, Applicants have nonetheless amended claim 1 to recite, in relevant part, “wherein the protein is ~~neuronally active~~ inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay.” Support for the amendment is found, for example, in Example 9, at page 24, line 23 to page 25, line 27, and in Figures 9 and 10. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 2 is rejected under 35 U.S.C. §112, second paragraph as indefinite and vague in the recitation of “said amino acid sequence.” The Office Action asks “What does this refer to? Is ‘said amino acid sequence’ referring to SEQ ID NOs: 1-12 or to any amino acid sequence having 95% identity to SEQ ID NO: 1-12?”

Applicants have amended claim 2 to recite, in relevant part, “which comprises at least one fragment of ~~said amino acid sequences having one of~~ SEQ ID NO: 1 or said amino acid sequence having at least about 95% sequence identity thereto, said fragment having at least one N-terminal, C-terminal and/or internal deletion.” Applicants believe the amendment makes clear

what it is that is being referred to. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §112, First Paragraph:

A. Written Description:

Claims 1, 2 and 21 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action states the following:

These claims are directed to an isolated protein having 95% identity to SEQ ID NO: 1. The specification does not contain any disclosure of the function of said protein except the statement as “neuronally active”, which cannot be a specific function, as well as all the protein sequences that are 95% identical to SEQ ID NO: 1. The genus of above protein molecules is a large variable genus with the potentiality of having many different structures as well as having many different unknown functions. Therefore, many functionally, unrelated proteins or peptides are encompassed within the scope of these claims. The specification discloses only several species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants respectfully disagree.

First, Applicants have amended claim 1 herein to require that the subject protein inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay. This limitation requires the claimed protein to have a specific function in a specific assay. The possibility that the 95% identity language may encompass proteins having “many different structures as well as having many different unknown functions” is not relevant where the claim affirmatively requires the stated functional activity (i.e., the claimed protein inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay). That is, by its plain language, the claim only encompasses those proteins that, in addition to satisfying all other limitations of claim 1, also inhibit neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay.

The Office Action states that “the specification discloses only several species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.” However, the written description requirement does not require a description of every species within a chemical genus. See *Utter v. Hiraga*, 845F.2d 993, 998 (Fed. Cir. 1988) (“A specification may, within the meaning of 35 U.S.C. §112, P1, contain a written description of a broadly claimed invention without describing all species the claim encompasses.”). Further, the Federal Circuit held in *Enzo Biochem, Inc. v. Gen-Probe Inc.* that:

“the written description requirement can be met by ‘showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics’.” *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002).

The Written Description guidelines noted in the Office Action have the same requirements with respect to disclosure of structure, function, and combinations thereof. Applicants submit that the specification provides ample description of structures in correlation with function to place one of skill in the art in possession of the inventions of claim 1 as amended. Examples include the following:

- In Figure 1 and in the description of Figure 1 in the specification, human PRG-1 amino acid sequence is provided. The description of the Figure at page 14, line 33 to page 15, line 6 provides detailed structural information regarding the protein of SEQ ID NO: 1. Specifically, the description states “The first 300 amino acids are highly conserved among LPP family members.” One of skill in the art would understand that strong conservation tends to indicate structural importance for common activities. The description of Figure 1 also states “The other 400 amino acids (gray boxed sequence) of PRG-1 show no homologies to known sequences. The catalytic histidine is marked with an asterisk.” Thus, the description indicates to one of skill in the art that the other 400 amino acids are likely involved in function unique to the PRG-1 polypeptide. Further, the specification identifies a key histidine in the catalytic site, structure that necessarily corresponds to enzymatic function.

- The hydrophobicity plot of Figure 2 indicates intracellular versus membrane-associated structural portions of the PRG-1 polypeptide.

- The phylogenetic tree of PRG proteins and LPP-1 in Figure 2 provides further guidance for examining related proteins for clues as to structure and function in the PRG-1 of SEQ ID NO: 1.

- Figure 14 provides a diagram that sets out the limits of the various extracellular loops, transmembrane domains and intracellular loop domains of the PRG-1 polypeptide of SEQ ID NO: 1. The ordinarily skilled artisan would be able to use this information in predicting whether a given mutation would likely disrupt or maintain this basic structure, and corresponding function, of the molecule.

- At page 2, lines 16-31 the specification states:

Therefore, the present invention is directed at an isolated protein comprising the same or substantially the same amino acid sequence selected from the group consisting of human PRG-1, human PRG-2, human PRG-3, human PRG-4, mouse PRG-1, mouse PRG-2, mouse PRG-3, mouse PRG-4, rat PRG-1, rat PRG-2, rat PRG-3, and rat PRG-4 (depicted in SEQ ID NOs: 1 to 12), respectively, or a splice variant or a salt thereof. A protein having substantially the same amino acid sequence comprises proteins with at least about 95%, preferably at least about 96%, more preferably at least about 97%, more preferably with at least about 98% and most preferably with at least about 99% amino acid sequence identity. *The amino acid exchanges are preferably so called conservative changes meaning substitutions of, for example, a polar amino acid residue by another polar amino acid residue, of a acidic amino acid residue by another acidic amino acid residue or of a basic amino acid residue by another basic amino acid residue.* (Emphasis added)

The specification therefore teaches that preferred changes are conservative amino acid changes, and teaches what types of changes are considered “conservative.”

- At page 3, lines 8-15, the specification states:

A fragment within the meaning of the present invention refers to one of the proteins according to SEQ ID NOs: 1 to 12 bearing at least one N-terminal, C-terminal and/or internal deletion. The resulting fragment has a length of at least about 50, preferably of at least about 100, more preferably of at least about 150, more preferably of at least about 200, more preferably of at least about 250, more

preferably of at least about 300 and in case of human PRG-1 and PRG-2 or mouse PRG-1 and PRG-2 or rat PRG-1 and rat PRG-2, more preferably of at least about 350 and most preferably of at least about 400 amino acids.

Thus, the specification provides guidance with regard to preferred fragment lengths.

- At page 3, lines 17 to 32, the specification states:

Preferably, the fragment is an N-terminal fragment which comprises 330 amino acids or less as outlined above, which are highly conserved between, for example, PRG-1 and members of the family of LPP membrane-associated phosphatic acid phosphatase ecto-enzymes, which have six membrane spanning domains with their active site located on the external surface of the plasma membrane. This domain comprises preferably the catalytic region. For example, human PRG-1 carries a catalytic histidine at position 252, which is involved in the phosphatase activity of human PRG-1. Similarly human, mouse and rat PRG-3 comprises a domain highly homologous to human PRG-1, which in rat PRG-3 spans amino acids 210 to 212 and includes a histidine residue at amino acid 209. Therefore, in a preferred embodiment any N-terminal fragment of the proteins of the present invention comprises the catalytic site, preferably including the conserved His-residue. The fragment itself has preferably an amino acid sequence identity with hPRG-1, hPRG-2, hPRG-3, hPRG-4, mPRG-1, mPRG-2, mPRG-3, mPRG-4, rPRG-1, rPRG-2, rPRG-3, and rPRG-4, respectively, of at least about 95%, preferably of at least about 96%, more preferably of at least about 97%, more preferably of at least about 98%, more preferably of at least about 99% and most preferably of 100%.

Thus, the specification provides specific guidance regarding structure as it relates to function, including extracellular, transmembrane and intracellular domains of the PRG polypeptides, including PRG-1 (SEQ ID NO: 1), and the location and identity of catalytic amino acids in human as well as rat and mouse proteins.

- At page 4, the specification states:

[0008] The C-terminal cytoplasmic part of the PRG proteins is potentially involved in regulation of lipid phosphate phosphatase activity and/or signaling and, thus, a further preferred fragment comprises a C-terminal fragment, which comprises about 413 amino acids or less as outlined above and which comprises regions required for above activity of the PRG proteins. The fragment itself has preferably an amino acid sequence identity with hPRG-1, hPRG-2, hPRG-3, hPRG-4, mPRG-1, mPRG-2, mPRG-3, mPRG-4, rPRG-1, rPRG-2, rPRG-3, and rPRG-4, respectively, of at least about 95%, preferably of at least about 96%,

more preferably of at least about 97%, more preferably of at least about 98%, more preferably of at least about 99% and most preferably of 100%.

Thus, the specification spells out potential structure/function importance of the C-terminal cytoplasmic domain delineated in the previous paragraph and in Figure 14.

- At page 19, lines 6-28, the specification states:

Similar to other members of LPP-family *a hydrophobicity analysis of PRG-1 predicts 6 N-terminal membrane-spanning regions with a highly conserved phosphatase domain*. The analysis was done using the DNAsis for Windows Version 2.6; Hitachi Software Engineering Co. Hydrophobicity Analysis Submenu using the Kyte & Doolittle algorithm with all settings set to default values. *However, unlike the other members of this family the second type of the protein consists of a long hydrophilic domain of around 400 amino acids (FIG. 2). According to the structural models of LPP orientation in the membrane, this C-terminal extension is positioned on the cytoplasmic site and might thus play a role as a regulatory or signal transduction domain.* Beside the homology of the N-terminal part of the PRG-1 to other members of the LPP-family such as LPP-1 and the Drosophila cell migration modulator Wunen, GenBank searches revealed only one other related gene (genomic DNA sequence: GenBank acc. # NP.sub.--011255.11) for which we cloned the complete cDNA sequence and named it PRG-2. This gene shares the same C-terminal extension with partial sequence homology. *Thus, these genes represent a novel distinct subclass of the LPP-1 family. Amino acid residues which have been shown to be essential for ecto-enzyme activity in the LPP-1 class of proteins are conserved in PRG-1 N-terminal sequences (FIG. 1).* Database analysis of the C-terminal domains did not detect any significant similarities to any other protein or any other matches with known conserved domains (using ProDom and Swiss-Prot databases). A GenBank search for orthologous proteins showed that both genes are highly conserved in mammals (human/mouse>93%), and partial EST sequences indicate orthologous proteins in Xenopus and Zebrafish, whereas no significant homology for the C-terminal part could be found in the Drosophila or other invertebrate genome.

Thus, the specification teaches that according to structural models, the C-terminal cytoplasmic extension might play a role as a regulatory or signal transduction domain and emphasizes the conserved amino acids shown to be essential for ecto-enzyme activity in related proteins.

- In Example 10, at page 25, line 29 to page 26, line 34, the specification describes effects of the mutation of the catalytic histidine at amino acid 252 to lysine. The specification states at page 25, lines 24-29:

The mutation of the conserved catalytic histidine (His-252) to a lysine (PRG-1^{His→Lys}) a change which has been shown to completely abolish enzymatic function of the catalytic center of LPP-1 (N. Zhang, et al. (1997) *supra*) no longer prevented LPA-induced retraction of processes as achieved by the wt-construct. ***This shows that the conserved enzymatic domain of the LPP-1 family is necessary for PRG-1 function in attenuating LPA-induced neurite retraction.***

The specification thus describes the functional impact of changing the structure of the polypeptide of SEQ ID NO: 1 at the catalytic histidine.

In view of the above, Applicants submit that the specification provides rather detailed guidance with respect to structure and function of the protein of SEQ ID NO: 1 and related proteins and fragments. Given this description and ordinary skill in the art, one of skill in the art would readily envision the full scope of the claimed invention – that is, one of skill in the art would recognize that Applicants had possession of an isolated protein comprising an amino acid sequence of SEQ ID NO: 1 or an amino acid sequence having at least about 95% sequence identity thereto, wherein mutations in the sequences having at least about 95% sequence identity are located in a sequence portion selected from the group consisting of: a) the N-terminal fragment of 330 amino acids or less, including the catalytic region, and b) the C-terminal fragment of 413 amino acids or less, including a regulatory domain, and wherein the protein inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay, as of the filing of the application. Applicants therefore submit that the specification provides adequate description of structures as they correlate with function to demonstrate to one of skill in the art that Applicants were in possession of the invention as claimed in claim 1 as amended.

Further, in a case that is directly on point with respect to the instant claims, the Board of Patent Appeals and Interferences has held that claims reciting “amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: X” satisfies the written description requirement on the basis of structural similarity. In *Ex parte Olga Bandman, Neil C. Corley, and Purvi Shah* (Appeal No. 2004-2319, slip op., (B.P.A.I., January 6, 2005)), the claims under appeal recited, as a representative example:

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

- a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 1:
- and
- b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1.

In *Ex parte Bandman*, the specification provided the complete structure of SEQ ID NO: 1, and the Board noted that the genus encompassed by the claims is “limited to polypeptides comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 1.” The Board stated “While the examiner asserts that the specification provides no disclosure of any particular structure/function activity relationship in the single disclosed species, the examiner has not adequately explained and/or provided evidence to support that assertion.” The Board reversed the Examiner’s rejection for lack of written description on the basis of structural similarities recited in the claim itself – that is, there was no reason provided as to why a polypeptide that varied by less than 5% relative to the reference sequence would not be expected to have structure/function similar to the reference sequence. The Board thus established that 95% sequence identity is adequately described where, as for the instant claims, the full length reference sequence is described. Thus, a claim which recites 95% sequence identity was held to satisfy the written description requirement where:

- i) only one sequence - i.e., the 100% identical sequence of *Bandman*’s SEQ ID NO: 1 - was provided; and
- ii) no function *at all* was recited in the claim.

Applicants submit that the instant claims as amended *meet and exceed* the standard applied by the Board in *Ex parte Bandman*. That is, in addition to the “95% identity” language, the instant claims require that a protein falling under the claims “inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay.” Also in addition to the “95% identity” language, the claims even limit the location of sequence differences with respect to SEQ ID NO: 1. Specifically, the claim recites “wherein mutations in the sequences having at least about 95% sequence identity are located in a sequence portion selected from the group consisting of: a) the N-terminal fragment of 330 amino acids or less, including the catalytic region, and b) the C-terminal fragment of 413 amino acids or less, including a regulatory domain.” In that regard, the instant claims are *significantly* more constrained than those upheld by the Board in *Ex parte Bandman*. In view of the above, the claims as amended satisfy the

written description requirement. Reconsideration and withdrawal of the written description rejection is respectfully requested.

B. Enablement:

Claims 1, 2 and 21 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Office Action states:

Applicants also argue that with respect to the recited mutations of the proteins with at least about 95% sequence identity to SEQ ID NOS. 1, the techniques to generate such mutant proteins are well known to the ordinarily skilled artisan, and thus, practicing the invention as now claimed would not involve undue experimentation.

This is not found persuasive because the enablement problem here is “how to use” the mutants and variants encompassed by 5% variation of SEQ ID NO: 1, while a skilled artisan could make any protein with 95% identity to SEQ ID NO: 1, not all such variants can be used in the claimed method, and not all variants will have the desired activity and furthermore, the claim is not limited to these variants with activity.

As mentioned in the previous office action, Claim 1 and 2 are so broad as to encompass any neuronally active protein of SEQ ID NO: 1, which is 95% identical to SEQ ID NO: 1 or any protein which comprises at least one fragment having one N-terminal, C-terminal and/or internal deletion of the SEQ ID NO: 1 without any structural feature of said fragments. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins and fragments broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only several proteins.

The Office Action thus concludes that the specification does not adequately enable the instant claims. Applicants respectfully disagree.

First, claim 1 as amended is limited to those proteins that, in addition to satisfying the sequence limitations, also “inhibit[s] neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay.” Thus, the claim does not encompass “any” protein of at

least 95% sequence identity with SEQ ID NO: 1, but rather, only those with the specified function.

The Office action emphasizes that “the enablement problem here is ‘how to use’ the mutants and variants encompassed by 5% variation of SEQ ID NO: 1 not all such variants can be used in the claimed method, and not all variants will have the desired activity and furthermore, the claim is not limited to these variants with activity.” As noted above, the claims as amended *do* require specific function, and the specification clearly teaches an LPA-induced neurite retraction assay. Further, the possibility that a claim encompasses non-functional embodiments is not fatal to the enablement of the claim, so long as one of skill in the art can distinguish functional from non-functional embodiments without undue experimentation. See, e.g., *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976) and *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 700 F.2d 1569, 1577 (Fed. Cir. 1984). As discussed above, an assay for LPA-induced neurite retraction is described in detail in the specification. Thus, a skilled artisan can readily determine, using such an assay, whether a given sequence variant that meets the structural limitations of the claims satisfies the functional requirements of the claim.

In this regard, the Examiner’s attention is respectfully directed to the decision of the Board of Patent Appeals and Interferences decision in *Ex Parte David F. Mark et al.*, 12 U.S.P.Q.2d 1904 (BPAI 1989), which is on point with respect to the instant question of enablement. In *Ex parte Mark*, the claims centered on synthetic muteins of native proteins in which a cysteine residue is substituted by another amino acid, and in which such proteins retain the biological activity of the native protein. A representative claim read as follows:

1. A synthetic mutein of a biologically active native protein in which native protein has at least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

The Examiner in *Ex parte Mark* rejected claim 1 as lacking enablement. The Examiner stated in the Examiner’s Answer on Appeal:

Essentially, the position taken in the rejection is that it would require undue further experimentation to construct by recombinant methods (site specific mutagenesis) *the innumerable muteins encompassed by the instant claims* (claims

encompass modification of any protein which comprises a “non-essential” cysteine residue) *and to screen the muteins produced for any of those which exhibit biological activity after modification. (emphases added)*

The appellants in *Ex parte Mark* took the position that given the disclosure of the specification regarding substituting a nonessential cysteine residue with a neutral amino acid, the nonessential cysteine residues of any candidate protein could be identified and substituted in ten days employing the methods disclosed in the specification and the general knowledge in the art at the time the application was filed. It was reasoned that such limited amount of experimentation based on the disclosure in the specification and the success shown by three proteins does not constitute undue experimentation.

The Board of Patent Appeals and Interferences agreed with the appellants. Specifically, the Board stated:

“The record before us establishes that for a given protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutein which is within the claims on appeal.”

That is, the Examiner’s focus on “the innumerable muteins encompassed by the instant claims” was misplaced. Where the specification and knowledge available to those skilled in the art permit one of skill in the art to determine whether a given protein falls under the scope of the claims, e.g., whether a given mutein lacks a cysteine but retains native activity, the specification is enabling for claims encompassing those proteins.

The reasoning of the Board in *Ex parte Mark* is directly applicable to the claims at issue in the instant application. Specifically, the subject claims recite “An isolated protein comprising an amino acid sequence of SEQ ID NO: 1 or an amino acid sequence having at least about 95% sequence identity thereto……, and wherein the protein inhibits neurite retraction in a statistically significant manner in an LPA-induced neurite retraction assay.” The instant Office Action states that “while recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications including deletions at N-terminal, C-terminal and/or internal of a protein sequence, as encompassed by the instant claims, and the positions within a protein’s sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any

protein and the result of such modifications is unpredictable and the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” However, as discussed above with respect to the written description rejection, the specification provides ample description of structural features of the lipid phosphate phosphatase proteins exemplified by SEQ ID NO: 1 and variants encompassed by the claims. In addition, the instant specification, analogously to the specification in the subject application in the *Ex parte Mark* appeal, teaches an example of a specific assay for LPA-induced neurite retraction that permits one of skill in the art to determine whether a given sequence variant has the function required by the claims. Thus, one of skill in the art can routinely determine whether a given variant inhibits neurite retraction in an LPA-induced neurite retraction assay. Therefore, in accord with the analysis of the Board in *Ex Parte Mark*, the instant specification is enabling with respect to the proteins recited in and encompassed by the claims as amended.

Further with regard to enablement, the Examiner’s attention is respectfully directed to *Ex parte Olga Bandman et al.* (BPAI Appeal No. 2004-2319, 2004) discussed above with respect to the written description rejection. Also on appeal in that case was an enablement rejection stating:

The claimed invention encompasses any isolated polynucleotide encoding any polypeptide comprising any naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 (claim 3) and any isolated polynucleotide comprising any naturally occurring polynucleotide sequence that is at least 95% identical to the nucleotide sequence of SEQ ID NO: 2 (claim 12).

The rejection further stated:

The amount of experimentation to make the claimed polynucleotide is enormous and undue and entails selecting specific nucleotides to change (deletion, insertion, substitution or combinations thereof) in any polynucleotide to make a polynucleotide encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 or selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in the nucleotide sequence of SEQ ID NO: 2 to make a polynucleotide that has a nucleotide sequence that is at least 95% identical to SEQ ID NO: 2 and determining by assays whether the encoded polypeptide has malate dehydrogenase activity.”

The Board *reversed* the enablement rejection, stating “That argument is not agreed with because the examiner has not explained and/or provided evidence why a naturally occurring

polynucleotide sequence that is at least 95% identical to the polynucleotide sequence of SEQ ID NO: 2, or a naturally occurring polypeptide sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1 would not have malate dehydrogenase activity.” That is, at a level of 95% sequence identity to the specifically described species, it is reasonable to expect the protein to have similar activity to the species described in the specification, and the claim is therefore enabled in its full scope. A detailed reckoning of exactly which amino acids can be changed is not required when the claim recites 95% sequence identity (note that this is not “homology” language, but, rather, “identity”). This reasoning is directly on point with respect to the instant enablement rejection, in which the Office Action states:

“Claim 1 and 2 are so broad as to encompass *any* neuronally active protein of SEQ ID NO: 1, which is 95% identical to SEQ ID NO: 1 or *any* protein which comprises at least one fragment having one N-terminal, C-terminal and/or internal deletion of the SEQ ID NO: 1 without *any* structural feature of said fragments. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins and fragments broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein’s amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein’s sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins’ structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only several proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications including deletions at N-terminal, C-terminal and/or internal of a protein sequence, as encompassed by the instant claims, and the positions within a protein’s sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable and the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

The specification does not support the broad scope of the claims which encompass *any* neuronally active protein of SEQ ID NO: 1, which is 95% identical to SEQ ID NO: 1 or which comprises at least one fragment having one N-terminal, C-terminal and/or internal deletion of the SEQ ID NO: 1 because the specification does not establish: (A) regions of the protein structure which may be

modified without affecting its unknown activity; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying said polypeptide amino acid residues with an expectation of obtaining 'the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore, the rejection is maintained. (*Italics added*)

While the Office Action sets out a rationale for alleged unpredictability with respect to sequence variants in general, it does not explain why any protein of at least 95% identity to a reference protein would not be expected to have similar function to that reference protein. That is, at the high required level of identity, it is reasonable to expect a variant to have function similar to the reference protein. Assays described in the specification, and now even recited in the claims, can be used to determine which of the variants encompassed by the 95% identity requirement of the claims has the required function. Further, this says nothing of the requirements also in the claims with regard to where the variations can occur in those proteins that differ from SEQ ID NO: 1 – i.e., “in a sequence portion selected from the group consisting of: a) the N-terminal fragment of 330 amino acids or less, including the catalytic region, and b) the C-terminal fragment of 413 amino acids or less, including a regulatory domain.” Taken together, the specification adequately teaches how to make variants encompassed by the claims and how to test them for functional activity required by the claims without undue experimentation and with a reasonable expectation of success. Applicants submit that the specification satisfies the enablement requirement with respect to the claims as amended. Reconsideration and withdrawal of the enablement rejection is respectfully requested.

In view of the above, all issues raised in the Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Should any fee deficiencies be associated with this submission, the Commissioner is authorized to debit such deficiencies to the Nixon Peabody Deposit Account No. 50-0850. Any overpayments should be credited to said Deposit Account.

Respectfully submitted:

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